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(71) Applicant : **MERCK & CO. INC.**
126, East Lincoln Avenue P.O. Box 2000
Rahway New Jersey 07065-0900 (US)

(72) Inventor : **Alberts, Alfred W.**
194 Sayre Drive
Princeton, NJ 08540 (US)
Inventor : **Lui, Chung Yuen**
423 Shoemaker Way
Lansdale, PA 19446 (US)
Inventor : **Repta, Arnold J.**
1208 Jana Drive
Lawrence, Kansas 66049 (US)
Inventor : **Scolnick, Edward M.**
811 Wickfield Road
Wynnewood, PA 19096 (US)

(74) Representative : **Barrett-Major, Julie Diane et al**
Merck & Co., Inc. European Patent
Department Terlings Park Eastwick Road
Harlow Essex CM20 2QR (GB)

(54) **Plasma cholesterol level lowering composition.**

(57) The instant invention is directed to a method for enhancing the lowering of plasma cholesterol level in a subject in need thereof which comprises the time-controlled administration of a nontoxic therapeutically effective amount of an HMG-CoA reductase inhibitor to said subject which surprisingly affords an equivalent or improved reduction of plasma cholesterol levels while significantly reducing the amount of HMG-CoA reductase inhibitor circulating in the bloodstream of the subject as compared to the same parameters when the oral administration of a conventional rapid release dosage form is utilized.

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BACKGROUND OF THE INVENTION

Hypercholesterolemia is known to be one of the prime risk factors for atherosclerosis and coronary heart disease, the leading cause of death and disability in Western countries.

There are agents known, however, that are very active antihypercholesterolemic agents which function by limiting cholesterol biosynthesis via inhibiting the enzyme, HMG-CoA reductase. These agents include the natural fermentation products, such as mevastatin, lovastatin and pravastatin, and semisynthetic analogs, such as simvastatin.

MEVACOR®, which contains lovastatin as the active agent, and ZOCOR®, which contains simvastatin as the active agent, are now commercially available for use as antihypercholesterolemic drugs. The reduction of the effective dosage amount which is anticipated to diminish the incidence of adverse experiences associated with these drugs would be extremely beneficial in view of the lifetime regimen of treatment of hypercholesterolemia.

Antihypercholesterolemic agents are useful for the treatment of arteriosclerosis, atherosclerosis, hyperlipidemia, familial hypercholesterolemia and like diseases in humans. They may be administered orally or parenterally in the form of a capsule, a tablet, an injectable preparation or the like. It is usually desirable to use the oral route. Doses may be varied, depending on the age, severity of hypercholesterolemia, body weight and other conditions of human patients but daily dosage for adults is within a range of from about 2 mg to 2000 mg (preferably 10 to 100 mg) which may be given in two to four divided doses. Higher doses may be favorably employed as required.

Utilizing controlled or sustained release technologies, a single administration of the indicated daily dosage amount delivers the drug to the patient over an extended period of time (i.e. 6 to 24 hours) to yield an equivalent or improved therapeutic effect while lowering the peak drug plasma levels. The response is apparently effected by improved hepatic extraction of the absorbed drug as the liver is the site of action of these antihypercholesterolemic agents. An additional benefit of this approach is the potential reduction in side effects associated with circulating drug.

Controlled delivery devices for the sustained release of therapeutically active agents are well known in the art. Generally, these devices may be characterized as either diffusion controlled systems, osmotic dispensing devices, dissolution controlled matrices, or erodible/degradable matrices.

U.S. Patent 3,538,214 discloses a diffusion controlled device in which a tablet core containing an active ingredient is surrounded by a water insoluble coating which contains a film modifying agent soluble in the external fluids in the gastrointestinal tract.

An example of an osmotic device is described in U.S. Patents 3,845,770 and 3,916,899 which is a core composition of an active agent and an osmotically effective solute which is enclosed by an insoluble semipermeable wall having a release means. Numerous modifications to these types of delivery devices have been described in the art in an effort to improve their release characteristics. U.S. Patents 4,256,108; 4,160,452; 4,200,098, 4,285,987, 4,327,725, and 4,612,008 disclose such improved delivery devices.

U.S. Patent 4,851,228 and co-pending U.S. Patent Application Serial No. 073,781, filed July 15, 1987 disclose systems which comprise an inner core compartment of osmotically active composition surrounded by an enclosing controlled porosity wall material that is substantially permeable to both solute and external fluid. These systems are osmotic dispensing devices for a broad range of therapeutically active agents. Co-pending U.S. Patent Application Serial No. 348,099, filed May 1, 1989 discloses such a delivery system which is controlled through the influence of a controlled release solubility modulator contained within the drug delivery device. U.S. Patent 4,795,644 also discloses such a delivery system which is controlled through the influence of a water insoluble, non-diffusible charged resin entity contained within the drug delivery device.

U.S. Patent 4,755,180 discloses a dosage form comprising a beneficial agent and a polymer coated osmotically effective solute for regulating the solubility of the beneficial agent.

Numerous examples of diffusion controlled and erodible/degradable devices are discussed in detail in Controlled Drug Delivery: Fundamentals and Applications, 2nd Edition, J.R. Robinson and V.H.L. Lee, Eds., Marcel Dekker, Inc., New York and Basel, 1987, and in Controlled Drug Delivery: Basic Concepts, Vols I and II, S.D. Brunk, Ed., CRC Press Inc., Boca Raton, FL, 1983.

BRIEF DESCRIPTION OF THE INVENTION

The instant invention is directed to a method for enhancing the lowering of plasma cholesterol levels in a subject in need thereof which comprises the time-controlled administration of a nontoxic therapeutically effective amount of an HMG-CoA reductase inhibitor to said subject which surprisingly affords an equivalent or improved reduction of plasma cholesterol levels while significantly reducing the amount of HMG-CoA reductase

inhibitor circulating in the bloodstream of the subject and thereby reducing the subject's peripheral or non-liver exposure to the inhibitor as compared to the same parameters when the oral administration of a conventional rapid release dosage form is utilized.

5 DETAILED DESCRIPTION OF THE INVENTION

One embodiment of this invention concerns a method for enhancing the lowering of plasma cholesterol levels in a subject in need thereof which comprises the time-controlled administration of a nontoxic therapeutically effective amount of an HMG-CoA reductase inhibitor to said subject utilizing a drug-delivery device for the controlled release of a therapeutically active ingredient into an environment of use.

The expression "time-controlled administration" as used herein broadly defines the controlled release of the HMG-CoA reductase inhibitor, in either the active form or pro-drug form, into the environment of use over a period of six (6) to twenty-four (24) hours. The time-controlled administration of the therapeutic effective amount of an HMG-CoA reductase inhibitor may be achieved by a variety of pharmaceutical procedures known to those skilled in the art. Among those procedures, but not inclusive, are diffusion controlled systems, osmotic devices, dissolution controlled matrices and erodible/degradable matrices.

One class of drug delivery device that is employed in the instant method includes the drug delivery devices which comprise a core composition comprising (a) a diffusible water soluble HMG-CoA reductase inhibitor, and (b) an osmotically effective agent surrounded by either (a) a water insoluble wall prepared from (i) a polymer material that is permeable to water but substantially impermeable to solute and (ii) 0.1 to 75% by weight, based on the total weight of (i) and (ii), of at least one water leachable pore forming additive dispersed throughout said wall; or (b) a substantially impermeable water insoluble wall surrounding said core composition and prepared from a semipermeable material substantially impermeable to core composition and permeable to the passage of an external fluid in the environment of use, with said wall (b) having a means for release of the therapeutic agent through the water insoluble wall.

Illustrative of this class of drug delivery device are those devices wherein the core composition of the drug delivery device comprises (a) a water insoluble, nondiffusible charged resin entity, and (b) a diffusible water soluble ionizable HMG-CoA reductase inhibitor carrying the same charge as said resin entity.

Also illustrative of this class of drug delivery device are those wherein the core composition of the drug delivery device comprises (a) a solubility modulating agent which is either (i) surrounded by a water insoluble coat containing at least one pore forming additive dispersed throughout said coat, or (ii) dispersed in a matrix substrate, and (b) a diffusible water soluble HMG-CoA reductase inhibitor.

A second embodiment of this invention relates to sustained release pharmaceutical compositions comprising:

- a) an HMG-CoA reductase inhibitor; and
- b) a hydroxypropyl methyl cellulose, such as methocel K15M, E5, E4M, K4M, K100M, and K100LV or a combination thereof.

Illustrative of this embodiment are those compositions wherein the HMG-CoA reductase inhibitor is a compound of formulae (I) and (II) as described below, and the hydroxypropyl methyl cellulose is selected from Methocel K15M, Methocel E5, Methocel E4M or a combination thereof. Further illustrating this embodiment are those compositions wherein the HMG-CoA reductase inhibitor comprises 4-17 weight percent and the hydroxypropyl methyl cellulose 19 to 43 weight percent of a unit dosage.

In one class are those compositions wherein the HMG-CoA reductase inhibitor comprises about 16-17 weight percent and the hydroxypropyl methyl cellulose 28 to 34 weight percent of a unit dosage. Further illustrating this class are those compositions wherein the hydroxypropyl methyl cellulose is selected from:

- a) about 20 to 21 weight percent Methocel E5 and about 8 to 9 weight percent Methocel K15M;
- b) about 8 to 9 weight percent E5 and about 24 to 25 weight percent Methocel K15M;
- c) about 33-34 weight percent Methocel K15M.

Specifically exemplifying this class are compositions selected from:

- a) about 16 to 17 weight percent lovastatin and about 20 to 21 weight percent Methocel K15M;
- b) about 16 to 17 weight percent lovastatin and about 8 to 9 weight percent Methocel E5 and about 24 to 25 weight percent Methocel K15M; or
- c) about 16 to 17 weight percent lovastatin and about 33 to 34 weight percent Methocel K15M.

In a second class are those compositions wherein the HMG-CoA reductase inhibitor comprises about 4 to 12 weight percent and the hydroxypropyl methyl cellulose about 19 to 43 weight percent of a unit dosage. Further illustrating this class are those compositions wherein the hydroxypropyl methyl cellulose is selected from:

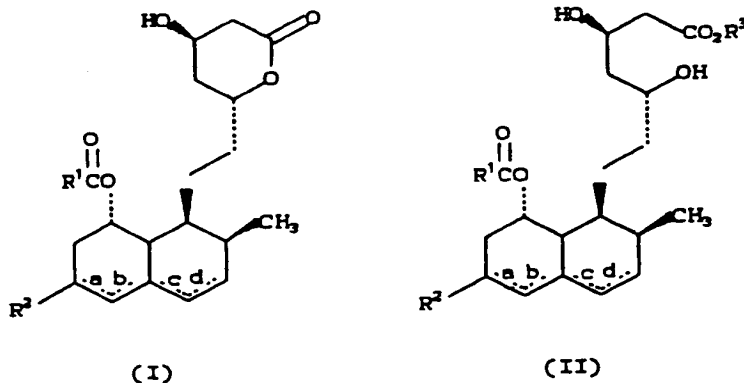
- a) about 38 to 40 weight percent Methocel K15M;

- b) about 19 to 20 weight percent E4M;
c) about 42 to 43 weight percent Methocel K15M.

Specifically exemplifying this class are compositions selected from:

- a) about 4 to 5 weight percent simvastatin and about 19 to 20 weight percent Methocel E4M;
b) about 4 to 5 weight percent simvastatin and 38-40 weight percent Methocel K15M;
c) about 11-12 weight percent simvastatin and about 19-20 weight percent Methocel E4M;
d) about 11 to 12 weight percent simvastatin and 42 to 43 weight percent K15M;
e) about 7 to 8 weight percent simvastatin and 39 to 40 weight percent Methocel K15M; or
f) about 7 to 8 weight percent simvastatin and 19 to 20 weight percent E4M.

The HMG-CoA reductase inhibitors which are utilized in the instant method include the compounds represented by the following structural formulae (I) and (II):



wherein:

R¹ is:

- (1) C₁₋₁₀ alkyl;
(2) substituted C₁₋₁₀ alkyl in which one or more substituent(s) is selected from
(a) hydroxy,
(b) C₁₋₆ alkoxycarbonyl,
(c) C₁₋₆ acyloxy,
(d) C₃₋₈ cycloalkyl, and
(e) phenyl and;

R² is:

- (1) methyl;
- (2) substituted C₁₋₁₀ alkyl in which the substituent is selected from:
 - (a) hydroxy, or
 - (b) C₁₋₆ acyloxy, and
- (3) C₁₋₆ alkoxy carbonyl and;
- (4) hydroxy; and

R^3 is:

- (a) hydrogen;
(b) C₁₋₅ alkyl;
(c) substituted C₁₋₅ alkyl in which the substituent is selected from
 (i) phenyl,
 (ii) dimethylamino, and
 (iii) acetylamino, and
(d) 2,3-dihydroxypropyl;

a, b, c and d each represent single bonds or one of **a, b, c and d** represents a double bond or both **a** and **c** or both **b** and **d** represent double bonds, provided that when **a** is a double bond, **R²** is methyl, substituted **C₁₋₁₀** alkyl or **C₁₋₈** alkoxy carbonyl; or a pharmaceutically acceptable salt thereof.

The compounds represent d by structural formula (I), and structural formula (II) wherein R³ is other than hydrogen have been described as the pro-drug form of the active moiety, the compounds represented by structural formula (II) wherein R³ is hydrogen.

One class of these HMG-CoA reductase inhibitor are those compounds of formula (I) or (II) wherein:

R¹ is C₁₋₁₀ alkyl; and

R² is

5 (1) methyl; or

(2) hydroxy.

Illustrative of this class of compounds are those selected from the group consisting of

(1) 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2,2-dimethylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoic acid;

10 (2) 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2(S)-methylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoic acid;

(3) 7-[1,2,6,7,8,8a(R)-hexahydro-2(S)-methyl 6(R)-hydroxy-8(S)-(2(S)-methylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoic acid; and

(4) 7-[1,2,6,7,8,8a(R)-hexahydro-2(S)-methyl 6(S)-hydroxy-8(S)-(2(S)-methylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoic acid

15 or a pharmaceutically acceptable salt thereof, specifically the tris(hydroxymethyl)methylammonium salt.

Also illustrative of this class of compounds are those selected from the group consisting of

(1) 6(R)-[2-[8(S)-(2(S)-methylbutyryloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (generically known as lovastatin); and

20 (2) 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (generically known as simvastatin).

The HMG-CoA reductase inhibitors which are utilized in the instant method are conveniently prepared according to known procedures specifically described in the literature. For example, U.S. Patent Nos. 4,231,938, 4,342,767, 4,444,784, and 4,346,227 disclose lovastatin, simvastatin and the ring opened dihydroxy acids thereof and pravastatin.

25 The drug-delivery devices which can be utilized in the method of this invention are conveniently prepared according to known procedures also specifically disclosed in the literature by utilizing the above described HMG-CoA reductase inhibitor as the active agent. For example, U.S. Patents 3,845,770, 3,916,899, 4,256,108; 4,160,452; 4,200,098, 4,285,987, 4,327,725, 4,612,008, 4,851,228 and 4,795,644 and co-pending U.S. Patent Applications Serial No. 073,781 filed July 15, 1987, Serial No. 348,099, filed May 1, 1989.

30 The following examples illustrate the method of the claimed invention and the preparation of drug-delivery devices which may be utilized in the method of this invention and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

35 EXAMPLE 1

7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2,2-dimethylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoic acid, an HMG-CoA reductase inhibitor which is the ring opened dihydroxy acid of simvastatin, was administered to dogs as the ammonium salt as either an oral bolus dose (rapid release) or as a continuous gastric infusion over 24 hours (simulated controlled release). In both cases, each dog received a dose of 10 mg/kg/day for 28 days of the above named HMG-CoA reductase inhibitor. Plasma cholesterol was determined throughout the entire study and drug-treatment levels compared to control cholesterol levels (pre-dosing) for each dog. Circulating plasma levels of the above named HMG-CoA reductase inhibitor were determined on Day 16 of each drug dosing period. The results are shown in Table 1.

Table 1: Plasma Cholesterol and Inhibitor Levels Following Oral Rapid Release and Gastric Infusion in Dogs.

	Mean Maximum Reduction In Plasma Cholesterol (percent, mean \pm SD)	Peak Circulating Plasma Drug Level (ng/ml, mean \pm SD)
Rapid Release	31 ^a	3575 ^a
Gastric Infusion	60 \pm 4.0 ^b	75 \pm 12.5 ^b
^a n = 1 dog ^b n = 4 dogs		

It is clear from the results (Table 1) that gastric infusion (simulated controlled-release) of the above named HMG-CoA reductase inhibitor affords improved lowering of cholesterol levels while resulting in decreased circulating levels of drug when compared to rapid release administration.

EXAMPLE 2

The same HMG CoA reductase inhibitor of Example 1 was administered to dogs as either an oral bolus dose (dry-fill capsule, rapid release) or as an oral controlled-release preparation. In both cases, each dog received a total daily dose of 100 mg equivalents of above named HMG-CoA reductase inhibitor. The resin modulated osmotic drug delivery device as prepared in Example 3, below, afforded controlled *in vitro* release of the drug over a 6-10 hour period. Serum cholesterol was determined throughout the entire study and drug-treatment levels compared to control cholesterol levels (pre-dosing) for each dog. Circulating inhibitor levels were determined on Day 16 of each drug dosing period. The results are shown in Table 2.

Table 2: Serum Cholesterol and Plasma Drug Levels Following Oral Rapid-Release and Controlled-Release of in Dogs

Dog No.	Percent Reduction in Serum Cholesterol		Peak Circulating Plasma Drug Level (ng/ml)	
	Rapid	Controlled	Rapid	Controlled
	Release	Release	Release	Release
01	8	26	571	203
03	20	30	1946	213
37	24	44	249	273
66	8	23	565	127
81	22	40	652	113
84	16	20	989	187
85	15	35	3940	319

These results (Table 2) indicate that controlled-release administration of above named HMG-CoA reductase inhibitor results in a consistent improvement in cholesterol lowering while significantly reducing circulating drug levels when compared to conventional rapid release oral bolus dosing.

EXAMPLE 3

A plurality of drug-delivery systems containing the HMG-CoA reductase inhibitor, 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2,2-dimethylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoate tris(hydroxymethyl)methylammonium salt, and Dow X 50X 8-100, and a negatively charged resin were

prepared. A wet granulation was made containing 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2,2-dimethylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoate tris(hydroxymethyl)methylammonium salt:tromethamine free base:mannitol:Dowex 50X 8-100:polyvinylpyrrolidone: butylated hydroxyanisole mixed in a 1:4.13:3.94:1.97:0.98:0.0024 ratio. The dried granules were lubricated with magnesium stearate (0.5% w/w) and compressed into 305 mg core compartments with a 3/8" standard concave tabletting die on a Stokes F-press tabletting machine. Next, a 350 µm thick microporous coat was applied to these cores. Cellulose acetate (54 g) having an acetyl content of 39% and 18 g cellulose acetate having an acetyl content of 32% were dissolved in a dichloromethane/methanol solvent blend. To this was added 52 g sorbitol and 14.4 g polyethylene glycol 400 dissolved in a water/methanol solvent blend. The composite solution contained water:methanol:dichloromethane in an approximate 1:10:15 ratio. This solution was sprayed onto cores in a Uni-Glatt fluidized bed coating machine. The *in vitro* release of 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2,2-dimethylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoate tris(hydroxymethyl)methylammonium salt from these devices into 900 ml volumes of 37°C, pH 1.2 HCl buffer and pH 8.0 phosphate buffer, both made isotonic with sodium chloride, was monitored using a USP Dissolution Method #2 apparatus with constant stirring at 50 rpm. Devices evaluated at pH 1.2 were transferred after 4 hours into the pH 8 media to simulate the variable pH conditions of the human gastrointestinal tract. HPLC was used to assay for drug. The release of 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2,2-dimethylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoate tris(hydroxymethyl)-methylammonium salt was prolonged for >14 hours with approximately 70% released at a nearly constant rate.

EXAMPLE 4

Core tablets were prepared as described in Example 3 substituting the anionic resin Amberlite IRP-64 for Dowex 50X 8-100. Cores (300 mg) were compressed in a 3/8" standard concave tabletting die on a Stokes F-press. A microporous coating was applied to the cores by fluidizing bed coating techniques. The coating solution was prepared in a water:methanol:methylene chloride (1:10:15) cosolvent containing 54 g cellulose acetate 398-30, 18 g cellulose acetate 320S, 52 g sorbitol, and 7.2 g polyethylene glycol 400. A microporous wall approximately 370 µm thick was applied.

EXAMPLE 5

A plurality of drug delivery systems containing Amberlite IRP-64 as a negatively charged resin are prepared as follows: a wet granulation is made containing the HMG-CoA reductase inhibitor, 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2,2-dimethylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoate tris(hydroxymethyl)methylammonium salt, tromethamine, mannitol, Amberlite IRP-64, polyvinylpyrrolidone, and butylated hydroxyanisole mixed 1:4:4:2:1:0.003, respectively. Core tablets are prepared by compressing 300 mg aliquots of the dried granulation into a 3/8" standard concave tabletting die with a single station Stokes F-press. Next, a semipermeable wall is applied to these cores. Cellulose acetate (18 g) having an acetyl content of 32% and 54 g cellulose acetate having an acetyl content of 39% are dissolved in a dichloromethane/methanol solvent blend. To this is added 20 g polyethylene glycol 400 as a flux enhancer/plasticizer dissolved in a water/methanol solvent blend. The composite solution contains water:methanol:dichloromethane in an approximate 1:10:15 ratio. This solution is sprayed onto the cores in a commercial Uni-Glatt fluidized bed coating machine. A wall 100 to 200 microns thick is applied. A hole 0.15 mm in diameter is drilled through the semipermeable wall to provide a means of release for the core composition.

EXAMPLE 6

A plurality of drug delivery devices are prepared with the HMG-CoA reductase inhibitor, 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2(S)-methylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoate tris(hydroxymethyl)methylammonium salt and the negatively charged resin amberlite IRP-64. A wet granulation is made containing 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-(2(S)-methylbutyryloxy)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoate tris(hydroxymethyl)methylammonium salt, tromethamine, mannitol, Amberlite IRP-64, polyvinylpyrrolidone, and butylated hydroxyanisole mixed 1:4:4:2:1:0.003, respectively. Core compartments are made by compressing 300 mg aliquots of the dried granules into a 3/8" standard concave tabletting die as in Example 3. Next, a microporous wall is applied. Cellulose acetate (36 g) having an acetyl content of 39% and 36 g cellulose acetate having an acetyl content of 32% are dissolved in an acetone/methanol solvent blend. To this is added 54 g nicotinamide as pore former and 40 g polyethylene glycol 400 as a flux enhancer/plasticizer dissolved in methanol. This solution is sprayed

onto the cores in a Uni-Glatt fluidized bed coating machine to form a microporous wall 100 microns thick. This microporous wall is then covered by a semipermeable wall as described in Example 5 with a hole 0.15 mm in diameter drilled through both the microporous and semipermeable walls.

5 EXAMPLE 7

A plurality of core tablets are prepared as described in Example 3. These cores are coated with a semipermeable wall 200 microns thick containing a drilled 0.15 mm diameter hole as described in Example 5. The devices are then spray coated with 100 micron thick layer of a water soluble mixture of polyvinylpyrrolidone and sorbitol mixed in a 1:25 weight ratio. This layer is then covered by a microporous wall 100 microns thick by spray coating a dichloromethane:methanol:water solution of a 1:1:1 blend of cellulose acetate having an acetyl content of 32%, cellulose acetate having an acetyl content of 39%, and sorbitol. The sorbitol is incorporated as a pore forming additive.

15 EXAMPLE 8

A tablet employing a matrix delivery system containing the therapeutic agent lovastatin (6(R)-[2-[8(S)-(2(S)-methylbutyryloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one) was prepared in the following sequence of steps: (The amounts given were used to prepare 1000 tablets)

- 20 1. Butylated hydroxyanisole (0.04 g) was dissolved in SD3A anhydrous alcohol (12.6 g);
2. The resulting solution was mixed with an amount of distilled water such that the v/v ratio of alcohol to water was 25/75;
3. Klucel LF (4.8 g) was dispersed in the alcohol/water mixture of step 2;
- 25 4. The following powders were added sequentially to a planetary mixer and mixed for 15 minutes:
Lactose (115.2 g), lovastatin (40 g), Avicel 101 (10 g), Methocel E5 (50 g), Methocel K15M (20 g);
5. With the mixer on, the solution of step 3 was added to the powder mix of step 4 over 1.5 to 2 minutes;
6. Granulation was continued for an additional 8 to 8.5 minutes and the massed powder tray dried overnight at 50°C;
- 30 7. The dried granules were then milled and lubricated with magnesium stearate (2.4 g, sieved through #60 mesh screen);
8. The lubricated granules were compressed into tablets by a F-press using 11/32 inch punches and die.

The release interval was approximately 8 hours with an 85% release.

Hydroxypropyl methylcellulose ethers such as Methocel E5, K15M, E4M, K4M, K100M and K100LV are available from the Dow Chemical Company. All other substances in this formulation are commercially available.

EXAMPLE 9 - 10

Tablets employing a matrix delivery system containing the therapeutic agent lovastatin were prepared following the procedure of Example 8 but substituting the following amounts in the composition:

	9 (in g)	10 (in g)
45 Butylated hydroxyanisole	0.04	0.04
SD3A	18	20
Klucel LF	4.8	4.8
50 Lactose	95.2	75.2
lovastatin	40	40
Avicel 101	20	40
Methocel E5	20	--
55 Methocel K15M	60	80
Magnesium Stearate	2.4	2.4

The formulation of Example 9 provided a release interval of 14 hours (85%) while that of Example (10) gave an 85% release over 18 hours.

Example 11

A tablet employing a matrix delivery system containing the therapeutic agent simvastatin (6(R)-[2[8(S)-(2,2-dimethylbutyryloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one) was prepared in the following sequence of steps: (The amounts given were used to prepare 1000 tablets)

1. Butylated Hydroxy Anisole (BHA) (0.04 g) was dissolved in ethanol (20 g).
2. Ascorbic Acid (5.0 g) and Citric Acid Monohydrate (2.50 g) were dissolved in water (60 g) and the aqueous solution slowly added to the ethanolic solution of step 1 with stirring.
3. Simvastatin (10.0 g) Microcrystalline Cellulose (Avicel PH101) (10.0 g), lactose (126.46 g), Hydroxypropyl Cellulose (HPC LF-NF)(4.0 g) and Hydroxypropylmethyl Cellulose E4MCR (Methocel E4MCR)(40.0 g) were blended in a high shear mixer.
4. The final solution of step 2 was added to the powder mix of step 3 with mixing.
5. The moist granules were dried by fluid bed drying for one hour.
6. The dried granules were then milled to remove any large agglomerates and then blended with Magnesium Stearate (2.0 g) and compressed using a tablet press.
7. The resulting tablets were film coated with an aqueous suspension of HPMC (6 cps)(1.65 g), HPC LF-NF (1.65 g), titanium dioxide (1.50 g) and purified talc (0.60 g) using a uniglatt column coater.

The release interval was approximately 5 hours with a 85% release.

The film coating in this example and in Examples 12-16 is not intended to modify the release of simvastatin. Throughout this specification and claims it should be understood that a CR (controlled release) grade methocel such as K15CR or E4MCR may be employed in place of the non-CR grade such as K15M or E4M.

Examples 12-14

Tablets employing a matrix delivery system containing the therapeutic agent simvastatin were prepared following the procedure of Example 11 but substituting the following amounts in the composition.

		<u>12</u>	<u>13</u>	<u>14</u>
		(amounts in grams)		
5	BHA	0.04	0.07	0.07
	Ethanol	20	35	35
	Ascorbic Acid	5.0	10.0	10.0
	Citric Acid Monohydrate	2.5	5.0	5.0
10	Water	60	105	105
	Simvastatin	10.0	40.0	40.0
	Avicel PH101	10.0	20.0	20.0
15	lactose	86.46	194.43	104.43
	HPC-LF-NF	4.0	7.0	7.0
	Methocel E4MCR	-	70.0	-
	Methocel K15MCR	80.0	-	160.0
20	Magnesium Stearate	2.0	3.5	3.5
	<u>Coating</u>			
25	HPMC 6 cps	1.65	3.30	3.30
	HPC LF-NF	1.65	3.30	3.30
	Titanium dioxide	1.50	3.00	3.00
30	Talc	0.60	1.20	1.20

The formulation of Example 12 provided a release rate of 15 hours (80%), that of Example 13 was 8 hours (80%) and Example 14 gave 18 hours (80%).

35 Examples 15-16

Tablets employing a matrix delivery system containing the therapeutic agent simvastatin are prepared following the procedure of Example 11 but substituting the following amounts in the composition.

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	15 (in grams)	16 (in grams)
BHA	0.05	0.05
Ethanol	25	25
5 Ascorbic Acid	5.0	5.0
Citric Acid Monohydrate	2.5	2.5
Water	75	75
10 Simvastatin	20.0	20.0
Avicel PH101	12.5	12.5
lactose	102.45	152.45
HPC-LF-NF	5.0	5.0
15 Methocel K15MCR	100.0	-
Methocel E4MCR	-	50.0
Magnesium Stearate	2.5	2.5
20 <u>Coating</u>		
HPMC 6cps	1.65	1.65
HPC LF-NF	1.65	1.65
25 Titanium dioxide	1.50	1.50
Talc	0.60	0.60

30 One of ordinary skill will recognize that other diluents, antioxidants, binders and lubricants may be substituted, with equivalent results, for those specifically listed in the above examples.

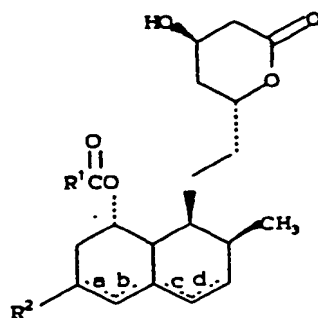
Illustrative of such diluents are lactose, dicalcium phosphate, Avicel, and sucrose.

Antioxidants/stabilizers may be selected from BHA, BHT, ascorbic acid, and citric acid. Example of possible binders are pregelatinized starch, PVP, celluloses, starch paste, and sucrose. Lubricants may be selected from 35 magnesium stearate, silicon dioxide, stearic acid, and hydrogenated vegetable oils.

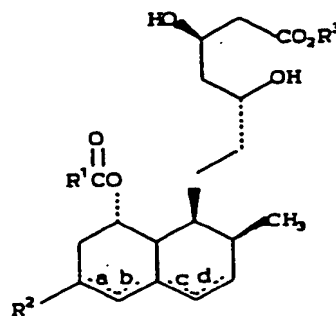
Where a weight of a unit dosage is referred to such weight implies the weight of a unit administered dose including active agent, carrier base, diluent, antioxidant, binder, lubricant, and any film coating.

40 Claims

1. A sustained release pharmaceutical composition comprising:
 - a) an HMG-CoA reductase inhibitor selected from compounds of formulae (I) and (II):



(I)



(II)

wherein:

R¹ is

- (1) C₁₋₁₀ alkyl;
- (2) substituted C₁₋₁₀ alkyl in which one or more substituent(s) is
 - (a) hydroxy,
 - (b) C₁₋₅ alkoxy, carbonyl,
 - (c) C₁₋₅ acyloxy,
 - (d) C₃₋₈ cycloalkyl, and
 - (e) phenyl and;
- (3) C₃₋₈ cycloalkyl;

R² is

- (1) methyl;
- (2) substituted C₁₋₁₀ alkyl in which the substituent is
 - (a) hydroxy, or
 - (b) C₁₋₅ acyloxy, or
- (3) C_{1,5} alkoxy, carbonyl or;
- (4) hydroxy; and

R³ is:

- (a) hydrogen;
 - (b) C₁₋₅ alkyl;
 - (c) substituted C₁₋₅ alkyl in which the substituent is
 - (i) phenyl,
 - (ii) dimethylamino, or
 - (iii) acetylamino, or
 - (d) 2,3-dihydroxypropyl;
- a, b, c and d each represent single bonds or one of a, b, c and d represents a double bond or both a and c or both b and d represent double bonds, provided that when a is a double bond, R² is methyl, substituted C₁₋₁₀ alkyl or C₁₋₅ alkoxy, carbonyl; and
- pharmaceutically acceptable salts thereof.
- b) a hydroxypropyl methylcellulose selected from Methocel K15M, Methocel E5, Methocel E4M or a combination thereof.

2. A composition of Claim 1 wherein the HMG-CoA reductase inhibitor comprises 4-17 weight percent and the hydroxypropyl methylcellulose 19 to 43 weight percent of a unit dosage.
3. A composition of Claim 2 wherein the HMG-CoA reductase inhibitor comprises about 16 to 17 weight percent and the hydroxypropyl methylcellulose about 28 to 34 weight percent of a unit dosage.
4. A composition of Claim 3 wherein the hydroxypropyl methylcellulose is selected from:
 - a) about 20 to 21 weight percent Methocel E5 and about 8 to 9 weight percent Methocel K15M; or
 - b) about 8-9 weight percent Methocel E5 and about 24 to 25 weight percent Methocel K15M; or
 - c) about 33-34 weight percent Methocel K15M.
5. A composition of Claim 3 comprising: from about 16-17 weight percent HMG-CoA reductase inhibitor; 28 to 34 weight percent hydroxypropyl methylcellulose; 47 to 52 weight percent diluent; 0.01 to 0.02 weight percent antioxidant; 1.9 to 2.1 weight percent binder and about 1 weight percent lubricant.
6. A composition of Claim 4 wherein the HMG-CoA reductase inhibitor is lovastatin.
7. A composition of Claim 6 selected from:
 - (a) about 16 to 17 weight percent lovastatin and about 20 to 21 weight percent Methocel E5 and about 8 to 9 weight percent Methocel K15M; or
 - (b) about 16-17 weight percent lovastatin and about 8 to 9 weight percent Methocel E5 and about 24 to 25 weight percent Methocel K15M; or
 - (c) about 16-17 weight percent lovastatin and about 33 to 34 weight percent Methocel K15M.
8. A sustained release pharmaceutical composition of Claim 7 which comprises:

from about 16-17 weight percent lovastatin; 47-48 weight percent lactose; 4.0-4.2 weight percent Avicel PH101; 0.010-0.020 weight percent butylated hydroxyanisole; 20.5 to 20.7 weight percent Methocel E5; 8.2-8.4 weight percent Methocel K15M; 1.9-2.1 weight percent Klucel KF; and about 1 weight percent magnesium stearate.

- 5 9. A sustained release pharmaceutical composition of Claim 7 which comprises:
from about 16-17 weight percent lovastatin; 39-40 weight percent lactose; 8.2-8.4 weight percent Avicel PH101; 0.010-0.020 weight percent butylated hydroxyanisole; 8.2-8.4 weight percent Methocel E5; 24.7-24.9 weight percent Methocel K15M; 1.9-2.1 weight percent Klucel KF; and about 1 weight percent magnesium stearate.
- 10 10. A sustained release pharmaceutical composition of Claim 7 which comprises:
from about 16-17 weight percent lovastatin; 31-32 weight percent lactose; 16.4-16.6 weight percent Avicel PH101; 0.010-0.020 weight percent butylated hydroxyanisole; 33-34 weight percent Methocel K15M; 1.9-2.1 weight percent Klucel KF; and about 1 weight percent magnesium stearate.
- 15 11. A composition of Claim 2 wherein the HMG-CoA reductase inhibitor comprises about 4 to 12 weight percent and the hydroxypropyl methylcellulose about 19 to 43 weight percent of a unit dosage.
- 20 12. A composition of Claim 11 wherein the hydroxypropyl methylcellulose is selected from:
(a) about 38-40 weight percent Methocel K15M;
(b) about 19-20 weight percent Methocel E4M;
(c) about 42-43 weight percent Methocel K15M.
- 25 13. A composition of Claim 10 wherein the HMG-CoA reductase inhibitor is simvastatin.
- 30 14. A composition of Claim 13 selected from:
(a) about 4-5 weight percent simvastatin, and about 19-20 weight percent Methocel E4M; or
(b) about 4-5 weight percent simvastatin, and 38-40 weight percent Methocel K15M; or
(c) about 11-12 weight percent simvastatin, and about 19-20 weight percent Methocel E4M; or
(d) about 11-12 weight percent simvastatin, and 42-43 weight percent K15M; or
(e) about 7-8 weight percent simvastatin, and 39-40 weight percent Methocel K15M; or
(f) about 7-8 weight percent simvastatin, and 19-20 weight percent E4M.
- 35 15. A composition of Claim 13 comprising: about 4 to 12 weight percent simvastatin; 19 to 43 weight percent hydroxypropyl methylcellulose; 34 to 66 weight percent diluent; 3 to 4.2 weight percent antioxidant/stabilizer; about 2 weight percent binder and about 1 weight percent lubricant.
- 40 16. A sustained release pharmaceutical composition of Claim 13 which comprises: about 5 weight percent simvastatin; about 61-62 weight percent lactose; about 5 weight percent Avicel PH101; about 3-4 weight percent antioxidant/stabilizer; about 19-20 weight percent Methocel E4M; about 1.9-2.1 weight percent Klucel KF; and about 1 weight percent Magnesium stearate.
- 45 17. A sustained release pharmaceutical composition of Claim 13 which comprises: about 5 weight percent simvastatin; about 42-43 weight percent lactose; about 5 weight percent Avicel PH101; about 3-4 weight percent antioxidant/stabilizer; about 38-40 weight percent Methocel K15M; about 1.9-2.1 weight percent Klucel LF; and about 1 weight percent Magnesium stearate.
- 50 18. A sustained release pharmaceutical composition of Claim 13 which comprises: about 11-12 weight percent simvastatin; about 53-55 weight percent lactose; about 5-6 weight percent Avicel PH101; about 4-5 weight percent antioxidant/stabilizer; about 19-20 weight percent Methocel E4M; about 1.9-2.1 weight percent Klucel LF; and about 1 weight percent Magnesium stearate.
- 55 19. A sustained release pharmaceutical composition of Claim 13 which comprises: about 11-12 weight percent simvastatin; about 28-30 weight percent lactose; about 5-6 weight percent Avicel PH101; about 4-5 weight percent antioxidant/stabilizer; about 42-43 weight percent Methocel K15M; about 1.9-2.1 weight percent Klucel LF; and about 1 weight percent Magnesium stearate.



European Patent
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EUROPEAN SEARCH REPORT

Application Number

EP 91 30 5745

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	US-A-4 915 954 (ALZA) * Claim 3; column 5, lines 1-24, 31-38, 55-58, 65-68; column 6, lines 1-16; column 8, line 43 * -----	1, 6, 13	A 61 K 9/20 A 61 K 9/22 A 61 K 9/48
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 04-09-1991	Examiner SCARPONI U.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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